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(21) International Application Number: PCT/US99/31025 (22) International Filing Date: 23 December 1999 (23.12.99) (30) Priority Data: 09/223,546 30 December 1998 (30.12.98) US (71) Applicant: MILLENNIUM PHARMACEUTICALS, INC. [US/US]; 75 Sidney Street, Cambridge, MA 02139 (US). (72) Inventor: HOLTZMAN, Douglas, A.; 821 Centre Street, #6, Jamaica Plain, MA 02130 (US). (74) Agents: CORUZZI, Laura, A. et al.; Pennie & Edmonds LLP, 1155 Avenue of the Americas, New York, NY 10036 (US).		(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). Published <i>With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>

(54) Title: SECRETED PROTEINS AND NUCLEIC ACIDS ENCODING THEM**(57) Abstract**

The invention provides isolated nucleic acid molecules, designated TANGO 128, TANGO 140, TANGO 197, TANGO 212, TANGO 213, TANGO 224 and TANGO 239. These nucleic acid molecules encode wholly secreted and transmembrane proteins. The invention also provides antisense nucleic acid molecules, expression vectors containing the nucleic acid molecules of the invention, host cells into which the expression vectors have been introduced, and nonhuman transgenic animals in which a nucleic acid molecule of the invention has been introduced or disrupted. The invention still further provides isolated polypeptides, fusion polypeptides, antigenic peptides and antibodies. Diagnostic, screening and therapeutic methods utilizing compositions of the invention are also provided.

clone deposited as any of ATCC 98999, 202171, 98965, and 98966, or a complement thereof, under conditions of hybridization of 6X SSC at 45°C and washing in 0.2 X SSC, 0.1% SDS at 65°C. The monoclonal antibodies can be human, humanized, chimeric and/or non-human antibodies.

5 The substantially purified antibodies or fragments thereof specifically bind to a signal peptide, a secreted sequence, an extracellular domain, a transmembrane or a cytoplasmic domain cytoplasmic membrane of a polypeptide of the invention. In a particularly preferred embodiment, the substantially purified antibodies or fragments thereof, the non-human antibodies or fragments thereof, and/or the monoclonal antibodies
10 or fragments thereof, of the invention specifically bind to a secreted sequence or an extracellular domain of the amino acid sequence of SEQ ID NOs:2, 5, 9, 12, 15, 18, 66, 21, 126. Preferably, the secreted sequence or extracellular domain to which the antibody, or fragment thereof, binds comprises from about amino acids 23-345 of SEQ ID NO:2 (SEQ ID NO:), from amino acids 1-146 of SEQ ID NO:5 (SEQ ID NO:35), from about amino
15 acids 28-301 of SEQ ID NO:9 (SEQ ID NO:), from about amino acids 19-553 of SEQ ID NO:12 (SEQ ID NO:), from about amino acids 23-271 of SEQ ID NO:15 (SEQ ID NO:), from about amino acids 29-458 of SEQ ID NO:18 (SEQ ID NO:), from about amino acids 29-874 of SEQ ID NO:9 (SEQ ID NO:) and amino acid residues 1 to 146 of SEQ ID NO:35.

20 Any of the antibodies of the invention can be conjugated to a therapeutic moiety or to a detectable substance. Non-limiting examples of detectable substances that can be conjugated to the antibodies of the invention are an enzyme, a prosthetic group, a fluorescent material, a luminescent material, a bioluminescent material, and a radioactive material.

25 The invention also provides a kit containing an antibody of the invention conjugated to a detectable substance, and instructions for use. Still another aspect of the invention is a pharmaceutical composition comprising an antibody of the invention and a pharmaceutically acceptable carrier. In preferred embodiments, the pharmaceutical composition contains an antibody of the invention, a therapeutic moiety, and a
30 pharmaceutically acceptable carrier.

 Still another aspect of the invention is a method of making an antibody that specifically recognizes TANGO 128, TANGO 140, TANGO 197, TANGO 212, TANGO 213, TANGO 224, and TANGO 239, the method comprising immunizing a mammal with a polypeptide. The polypeptide used as an immungen comprises an amino acid sequence
35 selected from the group consisting of: the amino acid sequence of any one of SEQ ID NOs:2, 5, 7, 9, 12, 15, 18, 21, 54, 57, 60, 63, 66, 69, 72, or an amino acid sequence encoded

What is claimed is:

1. An isolated nucleic acid molecule selected from the group consisting of:
 - a) a nucleic acid molecule comprising a nucleotide sequence which is at
5 least 55% identical to the nucleotide sequence of SEQ ID NO:1, 3, 4, 6, 8, 10, 11, 13, 14, 16, 17, 19, 20, 22, 38, 39, 53, 55, 56, 58, 59, 61, 62, 64, 65, 67, 68, 70, 71, 73, or the cDNA insert of the plasmid deposited with the ATCC as any of Accession Numbers 98999, 202171, 98966, 98965, or a complement thereof;
 - b) a nucleic acid molecule comprising a fragment of at least 300 nucleotides
10 of the nucleotide sequence of SEQ ID NO:1, 3, 4, 6, 8, 10, 11, 13, 14, 16, 17, 19, 20, 22, 38, 39, 53, 55, 56, 58, 59, 61, 62, 64, 65, 67, 68, 70, 71, 73, or the cDNA insert of the plasmid deposited with the ATCC as any of Accession Numbers 98999, 202171, 98966, 98965, or a complement thereof;
 - c) a nucleic acid molecule which encodes a polypeptide comprising the amino
15 acid sequence of SEQ ID NO:2, 5, 7, 9, 12, 15, 18, 21, 54, 57, 60, 63, 66, 69, 72, or amino acid sequence encoded by the cDNA insert of the plasmid deposited with the ATCC as any of Accession Numbers 98999, 202171, 98966, 98965;
 - d) a nucleic acid molecule which encodes a fragment of a polypeptide comprising the amino acid sequence of SEQ ID NO:2, 5, 7, 9, 12, 15, 18, 21, 54, 57, 60, 63,
20 66, 69, 72, or the polypeptide encoded by the cDNA insert of the plasmid deposited with the ATCC as any of Accession Numbers 98999, 202171, 98966, 98965, wherein the fragment comprises at least 15 contiguous amino acids of SEQ ID NO:2, 5, 7, 9, 12, 15, 18, 21, 54, 57, 60, 63, 66, 69, 72, or the polypeptide encoded by the cDNA insert of the plasmid deposited with the ATCC as any of Accession Numbers 98999, 202171, 98966, 98965; and
 - e) a nucleic acid molecule which encodes a naturally occurring allelic variant of a polypeptide comprising the amino acid sequence of SEQ ID NO:2, 5, 7, 9, 12, 15, 18, 21, 54, 57, 60, 63, 66, 69, 72, or the amino acid sequence encoded by the cDNA insert of the plasmid deposited with the ATCC as any of Accession Numbers 98999, 202171, 98966, 98965, wherein the nucleic acid molecule hybridizes to a nucleic acid molecule comprising
30 SEQ ID NO:1, 3, 4, 6, 8, 10, 11, 13, 14, 16, 17, 19, 20, 22, 38, 39, 53, 55, 56, 58, 59, 61, 62, 64, 65, 67, 68, 70, 71, 73, or a complement thereof under stringent conditions.
2. The isolated nucleic acid molecule of claim 1, which is selected from the group consisting of:
 - a) a nucleic acid comprising the nucleotide sequence of SEQ ID NO:1, 3, 4, 6,
35 8, 10, 11, 13, 14, 16, 17, 19, 20, 22, 38, 39, 53, 55, 56, 58, 59, 61, 62, 64, 65, 67, 68, 70, 71,

9. The isolated polypeptide of claim 8 comprising the amino acid sequence of SEQ ID NO:2, 5, 7, 9, 12, 15, 18, 21, 54, 57, 60, 63, 66, 69, 72.
10. The polypeptide of claim 8 further comprising heterologous amino acid sequences.
11. An antibody which selectively binds to a polypeptide of claim 8.
12. A method for producing a polypeptide selected from the group consisting of:
- 10 a) a polypeptide comprising the amino acid sequence of SEQ ID NO:2, 5, 7, 9, 12, 15, 18, 21, 54, 57, 60, 63, 66, 69, 72, or the amino acid sequence encoded by the cDNA insert of the plasmid deposited with the ATCC as any of Accession Numbers 98999, 202171, 98966, 98965;
- 15 b) a polypeptide comprising a fragment of the amino acid sequence of SEQ ID NO:2, 5, 7, 9, 12, 15, 18, 21, 54, 57, 60, 63, 66, 69, 72, or the amino acid sequence encoded by the cDNA insert of the plasmid deposited with the ATCC as any of Accession Number 98999, 202171, 98966, 98965, wherein the fragment comprises at least 15 contiguous amino acids of SEQ ID NO:2, 5, 7, 9, 12, 15, 18, 21, 54, 57, 60, 63, 66, 69, 72, or the amino acid sequence encoded by the cDNA insert of the plasmid deposited with the ATCC as any
- 20 of Accession Numbers 98999, 202171, 98966, 98965; and
- c) a naturally occurring allelic variant of a polypeptide comprising the amino acid sequence of SEQ ID NO:2, 5, 7, 9, 12, 15, 18, 21, 54, 57, 60, 63, 66, 69, 72, or the amino acid sequence encoded by the cDNA insert of the plasmid deposited with the ATCC as any of Accession Numbers 98999, 202171, 98966, 98965, wherein the polypeptide is
- 25 encoded by a nucleic acid molecule which hybridizes to a nucleic acid molecule comprising SEQ ID NO:1, 3, 4, 6, 8, 10, 11, 13, 14, 16, 17, 19, 20, 22, 38, 39, 53, 55, 56, 58, 59, 61, 62, 64, 65, 67, 68, 70, 71, 73, or a complement thereof under stringent conditions;
- comprising culturing the host cell of claim 5 under conditions in which the nucleic acid molecule is expressed.
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13. A method for detecting the presence of a polypeptide of claim 8 in a sample, comprising:
- a) contacting the sample with a compound which selectively binds to a polypeptide of claim 8; and
- 35 b) determining whether the compound binds to the polypeptide in the sample.

which binds to the polypeptide in a sufficient concentration to modulate the activity of the polypeptide.

22. A method for identifying a compound which modulates the activity of a
5 polypeptide of claim 8, comprising:
- a) contacting a polypeptide of claim 8 with a test compound; and
 - b) determining the effect of the test compound on the activity of the
polypeptide to thereby identify a compound which modulates the activity of the
polypeptide.

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